Magnesium supplements may enhance the effect of antihypertensive medications in stage 1 hypertensive subjects

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Abstract. Comprehensive analytical review of 44 human studies in 43 publications of oral Magnesium (Mg) therapy for hypertension (HT) shows Mg supplements may enhance the blood-pressure (BP) lowering effect of anti-hypertensive medications (medications) in Stage 1 HT subjects. 9 studies conducted on subjects treated with medications continuously ≥ 6 months (with ≤ 2-wk washout) resulted in significant decreases in both SBP and DBP with oral Mg supplements as low as 230 mg (10 mmol) per day. Twice this oral Mg dose, i.e. 460 mg/day, was required to significantly lower both SBP and DBP in 18 of 22 studies conducted on Stage 1 HT subjects either treatment-naïve or with their medication use interrupted ≥ 4 weeks within 6 months pre-study. Of the 4 remaining studies showing no BP change at these high Mg doses, two had large placebo effect, a third one had significant baseline discrepancies between Mg-test and placebo groups, and the fourth showed a significant decrease in DBP but not SBP. Thirteen studies on normotensive subjects, both treated and untreated with medications, showed no significant BP lowering effect with oral Mg therapy up to 25 mmol/day (607 mg). Conclusions: Mg supplements above RDA may be necessary to significantly lower high blood pressure in Stage I HT unless subjects have been continuously treated with anti-HT medications ≥ 6 months. Such medication use may lower by half the oral Mg dose needed to significantly decrease high blood pressure. Oral Mg therapy may have no effect in studies with normotensive subjects. Study of oral Mg therapy for severe or complicated hypertension has been neglected. Often the first cardiovascular risk factor to present, high blood pressure may be an early opportunity to correct poor Mg status and its possible complications including cardiovascular disease, respiratory diseases, and type 2 diabetes. Such preventive potential encourages quantification of these findings and testing of these hypotheses with a meta-analysis using categories elucidated by this preliminary study and finally would warrant a call for a prospective study.

Key words: magnesium, hypertension, blood pressure, anti-hypertension medications, oral magnesium therapy

Studies testing oral Mg therapy for hypertension have led to conflicting results. Thirteen clinical studies published between 1983 and 2009 showed a significant decrease in blood pressure (BP) with daily Mg supplements [1, 2, 4-8, 11, 22, 25, 26, 39, 40] while 19 similar studies during the same period did not [10, 12-14, 16, 17, 21, 27, 28, 30-38, 41]. Four studies during this same period reported mixed results [15, 24, 42, 43]. Four others showed a significant change in systolic blood pressure (SBP) but
not diastolic blood pressure (DBP) with Mg [3, 9, 19, 20], and another two showed decreases in DBP but not SBP [18, 23]. One paper showed decreases in both SBP and DBP without testing significance [29]. An analytical review of all these studies might extract knowledge from these seemingly contradictory results.

Background

A Meta-analysis of 12 of these studies found heterogeneity in results not explained by dose of Mg, baseline blood pressure or gender proportion of subject samples [44]. A second meta-analysis of 20 of these studies found a small overall reduction in blood pressure and an apparent dose-dependent effect of Mg [45]. Preliminary analysis using 16 of the cited studies showed Mg supplement dose to be an important factor in blood pressure results [46]. An expanded study using 32 of the citations pointed to subjects’ anti-hypertensive medication use as a second possible determinant in results [47] and revealed a third determinant – that oral Mg therapy does not significantly lower blood pressure in studies with normotensive subjects [ibid]. After publication of this preliminary and expanded work, eight additional studies were found and added to this current analytic review that compares all 43 publications with respect to daily Mg dose, use or non-use of medications and the hypertensive/normotensive status of subjects.

Examination criteria and categorization of studies

Sorting of studies as “treated” or “untreated” by medication status of subjects

Given published information that less than 6 months’ treatment with thiazide diuretics will not impact Mg therapy for high blood pressure [3, 16], each study was categorized as “treated” or “untreated” using the following criteria:
- studies on “treated” subjects were those where: all or most (> 50%) subjects’ anti-HT medication therapy was uninterrupted for at least 6 months by the end of their Mg supplementation period;
- studies on “untreated” subjects were those where: subjects were treatment naïve or all or most (> 50%) subjects’ anti-HT medication therapy was interrupted during the study or within 6 months pre-study.

Sorting of studies according to subjects’ “hypertensive” vs “normotensive” status at baseline

“Hypertensive” status was defined as blood pressure at or above Stage 1 Hypertension SBP and DBP values, i.e. 140/90 mmHg [48]. Studies with < 45.0% hypertensive subjects at baseline were categorized as “normotensive” studies. To determine the percentage of each study’s hypertensive subjects at entry, Z values for DBP > 90 mmHg (and SBP > 140 mmHg in unclear cases) were calculated for placebo groups and Mg-test groups using each group’s baseline mean and standard deviation for DBP and SBP.

Methods

Collection of studies

A PubMed search was undertaken for clinical studies of Mg supplements’ effect on blood pressure. Further publications were found from these articles’ references and included in the collection process. Two additional studies, suggested during peer review, were added.

Description of studies

Forty-three articles were found [1-43] that fit the selection criteria: studies of Mg supplementation at a designated daily dose with change in blood pressure as a measured outcome. Abstracts for all and full manuscripts for all but three [5, 10, 21] were retrieved. Two studies’ data appeared in multiple articles [35-37, 42, 43], and three publications included more than one study [15, 24, 27] (figure 1).

These 44 studies present a wide variety of design, length of study, number of subjects, form of Mg, dose of Mg, medication histories, hypertensive status of subjects, statistical analyses, and measuring/reporting of blood pressure results. This wide variety made a meta-analysis and/or Forest Plot, at this stage of investigation, full of extraneous decisions that could minimize results or require non-inclusion of some studies. Instead, it was decided to include all studies in an examination process as a preliminary step towards a categorized meta-analysis that might include all studies and maximize their collective information.

Using defined criteria, each of the 44 studies from these 43 articles were examined and categorized by the study examination process described below to ascertain studies’ subject stage of hypertension and medication status plus results of “decrease” or “no change” in blood pressure.

A. ROSANOFF
Figure 1. Flow chart for article examination and study categorization.
Sorting study results as “decrease” or “no change” in blood pressure by reviewing blood pressure results with set criteria

Each study’s blood pressure change was designated as a significant “decrease” or “no change”. For a study’s blood pressure change to be deemed a “decrease” the study’s Mg group had to show a statistically significant decrease in mean arterial pressure (MAP) or both diastolic (DBP) and systolic blood pressure (SBP) from its own baseline as well as from any control or placebo group. Any partial fulfillment of this outcome, e.g. significantly lower SBP but not DBP, was deemed “no change”.

Handling of cross-over designs: cross-over experimental design can minimize blood-pressure-lowering results for essential nutrient therapy since replenishment of Mg status can occur during Mg test periods that precede a placebo period [49]. Twelve of the 44 studies were cross-over design and of these, five did not report being corrected or tested for this possible carry-over effect. Results for these studies were recalculated where possible, eliminating from analysis placebo periods that followed a period of Mg therapy. In these recalculation, a statistically significant decrease (unpaired Student’s t-tests, alpha = 0.05) in both DBP and SBP from baseline (and placebo-before-Mg, if available) was required for that study’s result to be considered a “decrease”. All others were designated as “no change” result.

Grouping like studies and tabulating by ascending Mg dose

After examination of all 44 studies using the above criteria, each study was assigned to one of three groups:
- “hypertensive” subjects “treated” with anti-HT medications at least 6 months – 8 studies;
- “hypertensive” subjects “untreated” with anti-HT medications at least 6 months – 23 studies;
- “normotensive” subjects either “treated” or “untreated” with anti-hypertensive medications – 13 studies.

Finally, each of these three groups’ studies were tabulated by ascending daily Mg dose for analysis in tables 1-3.

Rationale for decisions on placement of individual studies as to hypertensive status or treatment category, as well as special considerations in blood pressure results, number of subjects, reporting of Mg dose, or experimental design are described in “Comments” in each table and in the supplementary online material.

Results

Oral Mg therapy was given to 1,556 subjects in 44 studies. Size of studies ranged from n = 7 to n = 227 subjects receiving Mg therapy. 299 subjects treated with Mg (19.2% of total) were in hypertensive populations with “treated” status; 487 (31.3% of total) were in hypertensive populations with “untreated” status. 770 (49.5% of total) were in normotensive subject populations, either “treated” or “untreated” by the criteria of this review.

Effect of Mg supplements on “treated” hypertensive subjects

Table 1 shows 8 studies [1-8] conducted on 299 hypertensive subjects “treated” at least 6 months with medications (beta-blockers, Ca channel blockers, ACE inhibitors, diuretics) and receiving Mg supplements. Mg daily doses ranged from 10 to 20 mmol (243-486 mg). All of these 8 studies showed a significant “decrease” in blood pressure by the criteria for this review.

Effect of Mg supplements on “untreated” hypertensive subjects

Table 2 groups 23 studies [9-28] conducted on 487 “untreated” (interrupted or treatment naïve) hypertensive subjects receiving Mg supplements into two parts: part A has 13 studies with Mg dose below 20 mmol/day while part B has 10 studies with Mg dose at or above 20 mmol/day.

Of the 13 studies at Mg doses < 20 mmol/day (table 2A), only one small study (study #11, n = 12) showed a “decrease” in blood pressure by the criteria of this review - the study having the shortest wash-out period for medications (2 wks). All other studies in table 2A showed “no change” in BP.

In contrast, six of the 10 studies in table 2B (≥ 20 mmol Mg/day) showed a significant “decrease” in blood pressure by the criteria of this review. Three of the four studies showing “no change” in BP were small studies (studies #27, #28, #31; n = 9; n = 17; n = 7, respectively) with questionable results (see supplementary online material). The remaining study in table 2B showing “no change” in blood pressure by the criteria of this review (study #23, [23]) was a large study (n = 47 receiving Mg) resulting in a significant decrease in DBP but an insignificant drop in SBP after 6 months of Mg therapy.
Table 1. Magnesium supplementation studies on treated hypertensive subjects, by ascending magnesium daily dose\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Study #</th>
<th>Mg dose (mmol/day)</th>
<th>BP results</th>
<th>Anti-HT medication status</th>
<th>Form of Mg</th>
<th>subjects (n)\textsuperscript{b}</th>
<th>Reference and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Decrease</td>
<td>Treated (Diuretics &gt; 1 yr)</td>
<td>MgCl\textsubscript{2}</td>
<td>22/42</td>
<td>Shafique \textit{et al.}, 1993 [1]</td>
</tr>
</tbody>
</table>
| 2       | 13.3              | Decrease   | Treated                   | Slow-Mag B\textsubscript{6} | 74 (92)        | Michon, 2002 \[2\]  
Final Blood Pressure result shows large decreases from baseline (-15-20 mmHg SBP and -5-9 mmHg DBP), but statistics unreported/unclear. Mg supplements were given to 74 hypertensive subjects on single medications for at least 6 months (ACE inhibitor, beta-blocker, Ca-channel blocker or diuretic) prior to baseline measurements. The 18 control hypertensive subjects were BP after Mg treatment period compared with baseline BP. |
| 3       | 15                | Decrease   | Treated (beta blockers)   | Aspartate  | 39            | Wirell \textit{et al.} 1994 \[3\]  
Recalculation of results, correcting for carry-over effect. This study reports no change in DBP and a decrease in SBP only when Mg supplementation followed the placebo period, by the criteria of this review, a "No Change" result. A cross-over design with uncorrected carry-over effect, this result's statistics were recalculated\textit{(see supplementary online material)}  
If a reliable use of t-test, this would indicate a "decrease" for study #3, but without the raw data necessary to confirm this result.  
Baseline Difference (unreported) in standing DBP & SBP between group starting with Mg and group starting with placebo |
| 4       | 15                | Decrease   | Treated (Diuretics > 5 yr) | Aspartate hydrochloride | 20            | Dyckner and Wester, 1983 \[4\] |
| 5       | 15 [79]           | Decrease   | Treated (losartan or verapamil) | Magnesio Boi | 35/70 | Ruiz-Lopez \textit{et al.}, 1999 \[5\] |
| 6       | 15.8              | Decrease   | Treated                   | Mg Pidolate | 9/18           | Paolisso \textit{et al.}, 1992 \[6\] |
| 7       | 18.5              | Decrease   | Treated                   | MgCl\textsubscript{2} | 40/79          | Guerrero-Romero and Rodriguez-Moran, 2009 \[7\]  
"All patients were on anti-hypertensive medication at least six months before the study." Personal Communication |
| 8       | 20                | Decrease   | Treated (assumed= 67% treated, duration unreported, w/ mono-or combo-therapy: Ca antag, beta-blocker, ACE Inhib, Alpha blockers &/or diuretics, no washout) | MgO | 60            | Kawano \textit{et al.}, 1998 \[8\]  
Trend for greater BP decrease in those on medications, men and elderly. Hypertensive status: No baseline BP measurements reported; Reported office SBP and DBP used to determine "hypertensive" status of this study\textit{(see supplementary online material)}. |

\textsuperscript{a} Studies reporting a majority (> 50\%) of subjects were taking anti-HT medication \textgreek{\geq} 6 months by study end.  
\textsuperscript{b} n = number of subjects in Mg group/Mg + placebo groups or number of subjects receiving Mg in crossover or non-placebo study.
**Table 2.** Magnesium supplementation studies on untreated hypertensive subjects, by ascending magnesium daily dose$^a$.

A) Subjects receiving < 20 mmol/day magnesium

<table>
<thead>
<tr>
<th>Study #</th>
<th>Mg dose mmol/day</th>
<th>BP results</th>
<th>Anti-HT medication status</th>
<th>Form of Mg</th>
<th>Subjects (n)$^b$</th>
<th>Citation (reference) and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>5</td>
<td>No change (decrease in SBP only)</td>
<td>Untreated</td>
<td>MgO</td>
<td>42/83</td>
<td>Borrello et al., 1996 [9] Reported at 10 mmol/day Mg (see supplementary online material, section of results for recalculation.)</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>No change</td>
<td>Untreated</td>
<td>Aspartate</td>
<td>12/25</td>
<td>Nowson and Morgan, 1989 [10]</td>
</tr>
<tr>
<td>11</td>
<td>10.5</td>
<td>Decrease (interrupted 2 wk washout 9.4 yrs mean HT diagnosis)</td>
<td>Interrupted</td>
<td>Dichloroaspartate-HCl</td>
<td>12</td>
<td>Sebeckova et al., 1992 [11] Minimum 2-wk washout is assumed to be from long term Ca channel blocker use (see supplementary online material of results)</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>No change</td>
<td>Untreated</td>
<td>Lactate &amp; citrate</td>
<td>45 (71)</td>
<td>Lind et al., 1991 [12] 71 subjects' blood pressure response with Mg supplementation. At baseline, 26 were normotensive and 45 had DBP &gt; 90 mm Hg. When analyzed separately, these 45 hypertensive subjects showed the same results as the whole study, i.e. &quot;no change&quot; in blood pressure with Mg supplement of 15 mmol per day.</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>No change</td>
<td>Untreated</td>
<td>Pidolate</td>
<td>7/14</td>
<td>Ferrara et al., 1992 [13] Results of this study are problematic, in part due to large placebo effect (see supplementary online material section of results)</td>
</tr>
<tr>
<td>14</td>
<td>15</td>
<td>No change</td>
<td>Untreated</td>
<td>Aspartate</td>
<td>30</td>
<td>Plum-Wirell et al., 1994 [14] Cross-over design uncorrected for carry-over effect: can minimize change in blood pressure</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>No change</td>
<td>Untreated</td>
<td>Mg(OH)$_2$</td>
<td>17</td>
<td>Widman et al., 1993 [15] Cross-over design uncorrected for carry-over effect: can minimize change in blood pressure. Part of &quot;titrated series&quot; with / Studies #29 and #30 (see supplementary online material section of results).</td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td>No change (Reclassified)</td>
<td>Untreated</td>
<td>Aspartate</td>
<td>36</td>
<td>Wirell et al., 1993 [16] This study has questionable &quot;untreated&quot; status (see supplementary online material section of results)</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>No change (interrupted 2 – 3 mos pre-study)</td>
<td>Untreated</td>
<td>Aspartate</td>
<td>17</td>
<td>Cappuccio et al., 1985 [17]</td>
</tr>
<tr>
<td>18</td>
<td>15.8</td>
<td>No change (decrease in DBP only)</td>
<td>Interrupted</td>
<td>MgCl$_2$</td>
<td>13/21</td>
<td>Reyes et al., 1984 [18] Large placebo effect</td>
</tr>
<tr>
<td>19</td>
<td>15.8</td>
<td>No change (decrease in SBP only)</td>
<td>Untreated</td>
<td>MgCl$_2$</td>
<td>7/14</td>
<td>Olhaberry et al., 1987 [19]</td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>No change (decrease in SBP only)</td>
<td>Untreated</td>
<td>MgCl$_2$</td>
<td>28</td>
<td>Purvis et al., 1994 [20] Untreated status assumed: study did not include subjects receiving diuretics or beta-blockers, but other anti-HT medications were not specified. Some subjects used oral hypoglycemics and all were diagnosed NIDDM</td>
</tr>
<tr>
<td>21</td>
<td>18.75</td>
<td>No change (assumed)</td>
<td>Untreated</td>
<td>MgO</td>
<td>8</td>
<td>Cohen et al., 1984 [21] Untreated status assumed; the 8 subjects were young and had a recent onset of essential hypertension</td>
</tr>
</tbody>
</table>

Total part A 283/359

(continued)
### B) Subjects receiving ≥ 20 mmol/day magnesium

<table>
<thead>
<tr>
<th>Study</th>
<th>Mg Dose</th>
<th>Change</th>
<th>Intervention</th>
<th>Mg Formulation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>20</td>
<td>Decrease</td>
<td>Interrupted 4 wks pre-study; 8.6 yrs mean HT diagnosis</td>
<td>MgCl$_2$ (with K)</td>
<td>Patki et al., 1990 [22]</td>
</tr>
<tr>
<td>23</td>
<td>20</td>
<td>No change</td>
<td>Untreated</td>
<td>Aspartate HCl</td>
<td>Wittman et al., 1994 [23]</td>
</tr>
<tr>
<td>24</td>
<td>25</td>
<td>Decrease</td>
<td>Untreated</td>
<td>MgO</td>
<td>Haga, 1992 [24]</td>
</tr>
<tr>
<td>25</td>
<td>25</td>
<td>Decrease</td>
<td>Interrupted - No medications 2 wks pre- and during study</td>
<td>MgO</td>
<td>Sanjuliani et al., 1996 [25]</td>
</tr>
<tr>
<td>26</td>
<td>25</td>
<td>Decrease</td>
<td>Interrupted - Untreated during study, at least 1 mo</td>
<td>MgO</td>
<td>Motoyama et al., 1989 [26]</td>
</tr>
<tr>
<td>27</td>
<td>25</td>
<td>No change</td>
<td>Untreated</td>
<td>Amino acid chelate</td>
<td>Walker et al., 2002 [27]</td>
</tr>
<tr>
<td>28</td>
<td>25</td>
<td>No change</td>
<td>Untreated</td>
<td>AA chelate + Hawthorne</td>
<td>Walker et al., 2002 [27]</td>
</tr>
<tr>
<td>29</td>
<td>30</td>
<td>Decrease</td>
<td>Untreated</td>
<td>Mg(OH)$_2$</td>
<td>Widman et al., 1993 [15]</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
<td>Decrease</td>
<td>Untreated</td>
<td>Mg(OH)$_2$</td>
<td>Widman et al., 1993 [15]</td>
</tr>
<tr>
<td>31</td>
<td>40</td>
<td>No change</td>
<td>Untreated</td>
<td>Aspartate</td>
<td>Zemel et al., 1990 [28]</td>
</tr>
</tbody>
</table>

Total part B: 204/282
Total table 2: 487/641

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1. **Untreated** studies include those reporting that a majority (> 50%) of subjects were treatment naïve or interrupted anti-hypertensive therapy within 6 months of end of study or taking anti-HT medications < 6 months.
2. $n$ = number of subjects in Mg group/Mg + placebo groups or number of subjects receiving Mg in crossover or non-placebo study.
Table 3. Magnesium supplementation studies on normotensive subjects, by ascending magnesium daily dose.

<table>
<thead>
<tr>
<th>Study #</th>
<th>Mg dose (mmol/day)</th>
<th>BP results</th>
<th>Anti-HT medication status</th>
<th>Form of Mg</th>
<th>(n)b</th>
<th>Citation (reference) and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>4.05</td>
<td>No statistical test</td>
<td>9/14 Untreated</td>
<td>Orotate</td>
<td>(14/17)</td>
<td>Sur and Maftei, 2006 [29] 9 of 14 subjects given Mg were normotensive. Result assignment not possible due to lack of statistical information (see supplementary online material section of results)</td>
</tr>
<tr>
<td>33</td>
<td>10.3</td>
<td>No change</td>
<td>Untreated</td>
<td>Mg(OH)₂</td>
<td>26</td>
<td>Doyle and Flynn, 1999 [30] Carry over effect in RBC Mg</td>
</tr>
<tr>
<td>34</td>
<td>12.3</td>
<td>No change</td>
<td>Unknown</td>
<td>MgO</td>
<td>75/155</td>
<td>Lee et al., 2009 [31]</td>
</tr>
<tr>
<td>35</td>
<td>12.5</td>
<td>No change</td>
<td>Treated</td>
<td>MgO</td>
<td>20/40</td>
<td>Henderson et al., 1986 [32] Authors report entry DBP significantly lower in Mg test group than control group. Reclassification of hypertensive status: inclusion criteria for this study was &quot;hypertension treated with potassium depleting diuretics for more than 6 months, DBP &lt; 105 mmHg. Since 69% of this study's Mg test group had DBP ≤ 90, &quot;normotensive&quot; by the criteria of this review, this study was reclassified as &quot;normotensive&quot; even though 75% had SBP &gt; 140</td>
</tr>
<tr>
<td>36</td>
<td>14</td>
<td>No change</td>
<td>Untreated</td>
<td>Lactate</td>
<td>50/153</td>
<td>Sacks et al., 1998 [33]</td>
</tr>
<tr>
<td>37</td>
<td>15</td>
<td>No change</td>
<td>Untreated</td>
<td>Aspartate hydrochloride</td>
<td>185/374</td>
<td>Sibai et al., 1989 [34] Pregnancy</td>
</tr>
<tr>
<td>39</td>
<td>15</td>
<td>No change</td>
<td>Untreated</td>
<td>Diglycine chelate (given with K or Ca)</td>
<td>65/96</td>
<td>Sacks et al., 1995 [38]</td>
</tr>
<tr>
<td>40</td>
<td>17 – 24</td>
<td>No change</td>
<td>Recalculated &quot;when necessary&quot;</td>
<td>Mg(OH)₂</td>
<td>23/33</td>
<td>Itoh et al., 1997 [39] By Student t-test (p &lt; 0.01), DBP at baseline was significantly lower in placebo (P) subjects than Mg supplemented subjects even though the paper reports no significant differences between P and Mg groups at baseline. Recalculation of BP results: this study reported a decrease in blood pressure as both SBP and DBP decreased significantly within the Mg group from their own baseline values. However, there was no significant difference between Mg group and placebo group for final SBP or DBP values. This paper also reports final SBP and DBP as % of baseline values and found % of baseline SBP for the Mg group significantly lower than that of the placebo group; this is not true for % of baseline DBP. By the criteria of this review, this study is designated &quot;no change&quot; in blood pressure.</td>
</tr>
<tr>
<td>41</td>
<td>20.6</td>
<td>No change</td>
<td>Untreated</td>
<td>MgO</td>
<td>20/40</td>
<td>Daly et al., 1996 [40] final DBP, SBP and MAP values did NOT differ significantly from placebo final values (see supplementary online material section of results). 48% HT (DBP &gt; 90) at baseline, 53% HT (SBP &gt; 140) at baseline.</td>
</tr>
</tbody>
</table>

(continued)
Effect of Mg supplements on normotensive subjects

Table 3 lists the 13 studies [24, 29-43] conducted on 770 Mg supplemented, largely normotensive subjects, both “treated” and “untreated” with medications. Daily doses of Mg supplement ranged from 4.05 to 25 mmol (98 to 600 mg). Study #32 [29] showed decreases in both SBP and DBP that were not statistically tested for which results according to the criteria of this review were not possible (see supplementary online material for more information). Of the 12 remaining studies, 11 studies – on 736 subjects receiving Mg – showed no statistically significant change in blood pressure by the criteria of this review, and one with 20 subjects (Study #44 [42, 43]) showed “mixed” results with a “decrease” in BP for 9 subjects who may have been mis-categorized “normotensive.” These 9 subjects had significantly higher baseline MBP compared to 11 “no change” subjects, but calculation of their possible hypertensive status by criteria of this review was not possible (see supplementary online material and comments in table 3 for additional details).

Discussion

This inclusive, comprehensive categorization and analysis implies potentially useful findings about hypertension studies with Mg therapy and suggests a categorized meta-analysis might quantify results and test the hypotheses generated by this preliminary study.

– Hypothesis 1: Stage 1 hypertension studies using subjects who are either treatment naïve or have their anti-HT medication use interrupted longer than 2 weeks need oral Mg doses above RDA values [61] (at or above 20 mmol/day) to show significant blood pressure lowering results. 19 studies on 407 subjects support this hypothesis, while 4 studies on 80 subjects do not (table 2). Three of these 4 studies (#27, #28 and #31 [27, 28]) treated 33 hypertensive subjects at doses of 25 and 40 mmol Mg/day but showed “no change” in blood pressure. These studies' problems, large placebo effect, significant differences at baseline, and possibility of “Mg-replete” subjects, have been outlined in the supplementary online material. The “Mg repleted subjects’ argument is speculation, not conclusion, and shows the high importance of a standard, clinical test for determining nutritional Mg status for full knowledge to come from future studies. Overall, these 3 studies include only 4.2% (33 out of 786) of subjects in all 31
studies on hypertensive subjects receiving Mg therapy in this review. Of those in the "Untreated" category at the higher, presumed effective Mg doses, they represent less than 20% (33/204 = 16.2%) of subjects and only 6.8% (33/487) of all subjects in the "untreated" category. One study of table 2 showed "no change" in blood pressure by the criteria of this review at ≥ 20 mmol/day of Mg supplement (study #23, [23]). This was a large study (n = 47 receiving Mg) showing a significant decrease in DBP, but a drop in SBP that was not statistically significant. Representing 23% of table 2B and 9.6% of all table 2 subjects, it may be an important finding that this study’s hypertensive status was borderline with only 46.4% of subjects having DBP > 90 at baseline. Meta-analysis of all table 2 results is needed to test hypothesis 1 and quantify any impact of these differences in study size, baseline BP values and degree of BP change.

– Hypothesis 2: Stage 1 hypertension studies using subjects on 6 months’ uninterrupted anti-HT medications need less than the RDA for Mg and only half of the minimum effective Mg dose (10 mmol rather than 20 mmol) necessary for "untreated" hypertensive subjects to successfully lower blood pressure. All eight studies on 299-subjects receiving Mg support this finding (table 1). What might uninterrupted use of these medications do, physiologically, to enhance the impact of nutritional Mg’s effect on high blood pressure? Do these medications physiologically lower an individual’s nutritional Mg requirement? If so, how? ACE inhibitors and beta-blockers act as Mg analogs and have been shown to "spare" or conserve Mg [62, 63] by decreasing Mg in the urine [64-67]. This may be at work in these medications’ tendency to conserve serum [68-70], lymphocyte [71], and intracellular [72] Mg. But long term use of thiazide diuretics can result in Mg (as well as potassium) loss [73], pointing to a different physiological mechanism. By whatever mechanism (s) anti-HT medications lower the effective Mg dose in hypertension studies, if real, the effect was still at work with a 2-week washout (see Study #11 [11], table 2A) and became nil with as little as a four-week washout period pre-study (see Study #18 [18], table 2A).

– Hypothesis 3: Oral Mg therapy studies on subjects with pre-hypertension or normal blood pressure, whether “treated” or “untreated” with anti-HT medications, do not show a significant lowering of blood pressure with oral Mg therapy – even at Mg doses as high as 25 mmol/day. Twelve statistically tested studies on 747 subjects support this finding (table 3); only 9 subjects in one/half of Study #44 [42, 43] do not. These 9 subjects showing a significant decrease in blood pressure with Mg therapy may have been "Hypertensive" by the criteria of this review (see supplementary online material). At any rate, they represent only 9/756 (excludes Study #32 [29]) = 1.2% of the “normotensive” subjects categorized in this review. Meta-analysis is the proper way to test Hypothesis 3. The 13 studies on “normotensive” subjects are by far the largest studies, representing half (49.5% = 770/1556) of all subjects receiving oral Mg therapy in these 44 blood pressure experiments. Their uncategorized inclusion in meta-analysis of Mg for hypertension studies could falsely minimize results and might best serve knowledge if meta-analyzed as a separate category.

The findings from this analytical review are not quantitative and the set criteria generalized (and possibly minimized) the results. For example, among results deemed "no change" by the criteria of this review, oral Mg therapy resulted in significant BP decreases only in DBP or only in SBP, while others showed significant decreases from their own baselines but not when compared with control groups. Still other studies had no control groups or unreliable controls, and only 16 of the 44 studies had n > 30 for a reliable statistical statement. Nonetheless, with these limitations in mind, this analysis suggests that:

For studies to show blood pressure lowering with Mg therapy, (a) hypertensive subjects may have to be in the majority, and (b) doses above 20 mmol/day Mg may be necessary unless subjects have been on uninterrupted anti-HT medication usage for at least 6 months.

Previous analysis without these findings may have tended to minimize the potential of oral Mg therapy for HT. Half (49.5%) of the 1,556 subjects receiving Mg therapy in these 44 studies were in subject populations "normotensive" at baseline by the criteria of this review, and another 18.2% of subjects were in studies given insufficient Mg doses given their medication status. This means that only 32.3% of the subjects in under half (40%) of the studies were actually "hypertensive" populations receiving adequate Mg therapy given their medication status. In a published meta-analysis, Jee et al. [45] used 20 of the studies, including 6 on normotensive subjects and 7 on subjects receiving < 20 mmol Mg without continuous 6-month anti-HT medication usage. Using such pooled results where only 27.8% of the subjects would be expected to show a blood pressure response to Mg therapy, we cannot be
surprised by the Jee et al. [45] meta-analysis conclusion that "Mg supplementation resulted in only a small overall reduction in BP." A similar situation appears with Dickinson et al. [44], a second meta-analysis where almost half (47.7%) of the subjects in the 12 studies used were in study designs not expected to respond to the Mg therapy by the findings of this current analytical review. These meta-analyses of "Mg therapy for hypertension" studies without categorization using knowledge of these current findings have perhaps minimized the potential of Mg therapy for the widespread malady of high blood pressure. A categorized meta-analysis using these findings is warranted.

These are statistical results from 44 randomized clinical studies in 22 countries. Inclusion and exclusion criteria of many limited most of the studies to hypertensive subjects with mild to moderate, uncomplicated Stage I hypertension; no published studies focusing on stage 2-3 hypertension with oral Mg therapy have been found. Thus, the findings of this analytical review do not predict possible outcome of Mg therapy for subjects with complicated or severe hypertension, an area completely open to and needing randomized clinical study. As with all statistically tested clinical trials, they do not predict a result for any one individual.

Conclusion

An inclusive, analytical review of 44 human studies from 43 publications shows that Mg supplements as low as 10 mmol (243 mg) per day may significantly lower blood pressure of stage 1, uncomplicated hypertensive subjects continuously treated 6 months or longer with anti-HT medications (including diuretics, beta-blockers, calcium channel blockers or ACE inhibitors). In contrast, daily Mg therapy at or above 20 mmol (486 mg) per day (i.e. above RDA), may be necessary to lower high blood pressure in studies on hypertensive subjects either treatment naïve or with at least a 4-week interruption in anti-HT medications. Past non-inclusive meta-analyses of these "Mg for hypertension" studies, along with the fact that the largest studies with Mg therapy for HT have been conducted on normotensive subjects, may have tended to minimize the potential of oral Mg therapy for HT. Given this minimized view of Mg’s potential, it is not surprising that studies of oral Mg therapy for severe (stage 2-3) hypertension were not found in the PubMed search. The findings of this analytical review suggest a categorized meta-analysis to test the following three hypotheses:

– stage 1 hypertension studies with subjects who are either treatment naïve or have their anti-HT medication use interrupted longer than 2 weeks need oral Mg doses ≥ 20 mmol/day (above RDA values) to show significant blood pressure lowering results;

– stage 1 hypertension studies with subjects on 6 months’ uninterrupted anti-HT medications need only 10 mmol Mg/day (less than RDA values for Mg) to significantly lower blood pressure;

– oral Mg therapy studies on subjects with pre-hypertension or normal blood pressure, whether "treated" or "untreated" with anti-HT medications, do not show a significant lowering of blood pressure with oral Mg therapy – even at Mg doses as high as 25 mmol/day.

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